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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,932	05/30/2001	Lijun Wu	MPI96-027CP2RCEM	9497

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,932	WU ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *158, 160-163, 166, 179, 181-184, 187, 200, 202-205 and 208* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *158, 160-163, 166, 179, 181-184, 187, 200, 202-205 and 208* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-3-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-28-05 has been entered.

2. The amendment filed 11-28-05 has been entered into the record and has been fully considered.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn.

5. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205 and 208 are pending.

Election/Restrictions

6. As previously of record, the claims are generic to a plurality of disclosed patentably distinct species comprising antibodies or antibody fragments that inhibit binding of chemokines a) MIP-1α, b) MIP-1β or c) RANTES to the human CCR5 receptor. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species of chemokine, i.e., either a) MIP-1α, b) MIP-1β or c) RANTES, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

This requirement is deemed necessary for examination purposes due to the introduction of the new limitations directed toward the specificity of the antibodies and antibody fragments to the different chemokines and arguments of record that the various chemokines are subject to different specific receptor binding parameters and hence the antibodies and antigen binding fragments thereof provide for different regional antibody binding/inhibiting specificity.

Applicant's election with traverse of RANTES in the reply filed on 7-19-04 is acknowledged. The traversal is on the ground(s) that the claims are drawn to antibodies and antibody fragments that bind CCR5 and not the different chemokines, that no arguments have been made that state the chemokines are subject to different specific receptor binding parameters or binding/inhibiting specificity, that the chemokine limitations are not new limitations and were previously searched and considered by the Examiner.

These arguments have been fully considered and are found to be persuasive. The restriction requirement is therefore withdrawn. However, Applicant's are put on

notice that distinction of the antibodies with respect to binding specificity may require reinstatement of the restriction (species) election requirement.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205 and 208 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are rendered obvious in view of the '625 patented claims directed to the HB-12366 (2D7) antibody, antigen binding fragment, antibody producing hybridoma, compositions and test kit with properties including all limitations as instantly recited. The disclosure of the species renders obvious the instant generic recitations.

Applicant's request in the response of 11-28-05 and 7-3-06 that the double patenting rejection be held in abeyance until such time that a notice of allowance is issued. No comments as to the correctness of the rejection have been noted.

Therefore rejection is maintained as set forth in MPEP 804, the "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Priority

9. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

As set forth in the new matter rejection below, claims 147-210 are directed to a subgenus of antibodies not supported by the specification or within the noted priority documents as originally filed. In the amendment of 2-4-04, Applicants state that no new matter is added and that support for the newly recited claims may be found within the specification at p. 11, lines 18-19; p. 12, lines 1-2; and page 59, line 24 through page

60, line 23. However, particular support for the new claim recitations is not found at these cited passages. Support is noted for antibodies as directed at p. 11-12, paragraph spanning. Further, support is noted for 5C7 as at p. 60. However, the claims are not directed to the genus of antibodies contemplated/supported in the specification as originally filed.

In particular, the claims are directed to a subgenus of CCR5 antibodies which binds "*human* CCR5" wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor.*" Yet these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a "*ligand*" and "*one or more functions mediated by CCR5 in response to the ligand.*" Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracelluar loop and inhibits HIV infection are not specifically noted.

Therefore the effective filing date with respect to instant claims is the instant filing date of May 30, 2001. Traversal of the priority determination should note where all claim limitations are specifically supported within Applicant's specification and the noted priority documents for the earliest effective filing date sought.

Applicants argue as extensively set forth in the 4-4-05 response, pp. 12-15, particularly noting the Table at pp. 14. Newly amended claims are particularly directed to antibodies or antigen binding fragments thereof which bind to the second extracellular

loop of a human chemokine receptor 5 (CCR5)..., as claimed. As noted, in the Table at p. 14 of the response, support is not found for such recitations prior to the disclosure of 6,528,625, filed July 11, 1997. Accordingly instant claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205 and 208 may only obtain the benefit of the **7-11-1997** date.

Applicants noted traversal at pp. 10-11 of the 11-28-05 response is considered moot in that the determination made is in accordance with the admission noted within the last paragraph of p. 11 noting that support is not found within the 1996 application for recitations with respect to "human" antibodies and "binds (to) the second extracellular loop" which are only noted in the 1997 application. All pending claims are drawn to recitations of "binds to the second extracellular loop" and accordingly all pending claims are evaluated with respect to the 7-11-1997 date.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205 and 208 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Li et al., (US Pat. No. 6,025,154, Feb. 15, 2000, IDS AE, see entire document) Li et al., (US Pat. No. 6,759,519, July 6, 2004), Raport et al., 1996 IDS Reference AW, Combadiere et al., 1996 IDS Reference AT3, and Samson et al., 1996 IDS Reference AV, as evidenced by Wu et al., J. Exp. Med. 1997; 186(8): 1373-1381, October, IDS (AS4), Atchison 1996, IDS Reference (AZ5) and Samson et al., J. Biol Chem., Oct. 1997, 272(40):24934-41 of record.

It is noted that US 6,025,154 and 6,759,519 are cumulative, therefore citations are with respect to the '154 patent except where noted.

The Li et al., references teach as extensively set forth in the record. Li et al. teach an antibody to human HDGNRI0 (see entire document, especially column 18). HDGNRI0 is the same protein as human CCR5 (see e.g., SEQ ID N0:2). Li et al. teach that the antibody may be a monoclonal, chimeric, single chain, humanized or human antibody, or fragments thereof that include Fab fragments or single chain Fv fragments (e.g., column 18, especially lines 1-36). Li et al. also teach compositions and kits comprising said antibodies (e.g., see column 13 in view of column 12).

Li et al. also teach assays for screening for antagonists of both ligand binding and receptor function associated with that binding (see especially columns 11-12). Li et al. also clearly contemplate that an antibody to CCR5 was such an antagonist and could

be produced and identified by the appropriate screen specifically for inhibition of binding, calcium flux and chemotaxis, all results of ligand binding at the binding site (see especially column 12 at lines 16-21 in view of columns 1 1-12 and 18).

In particular, Li teaches antibodies capable of inhibiting chemotaxis, a function of chemokine binding at the CCR5 receptor, and that inhibit ligand binding and receptor function, see in particular, column 2, lines 65-67, columns 11-12. In addition the patents teach transmembrane structure of the GPCR, particularly of extracellular portions, denotes soluble forms of the receptor that are the extracellular portions separate from the cytoplasmic and transmembrane domains and antibodies to such fragments or portions as particularly claimed within the '519 patent.

As in US 6,025,154, Detailed Description Text (9):
"The polynucleotides may also encode for a soluble form of the G-protein chemokine receptor polypeptide which is the extracellular portion of the polypeptide which has been cleaved from the TM and intracellular domain of the full-length polypeptide of the present invention."
Detailed Description Text (98):
The polypeptides, their fragments or other derivatives, or analogs thereof, or cells expressing them can be used as an immunogen to produce antibodies thereto. These antibodies can be, for example, polyclonal or monoclonal antibodies. The present invention also includes chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library. Various procedures known in the art may be used for the production of such antibodies and fragments.
Detailed Description Text (99):
Antibodies generated against the polypeptides corresponding to a sequence of the present invention can be obtained by direct injection of the polypeptides into an animal or by administering the polypeptides to an animal, preferably a nonhuman. The antibody so obtained will then bind the polypeptides itself. In this manner, even a sequence encoding only a fragment of the polypeptides can be used to generate antibodies binding the whole native polypeptides. Such antibodies can then be used to isolate the polypeptide from tissue expressing that polypeptide.

Li et al., does note that chemokines are expected to bind at the CCR5 receptor but are silent as to the preferred chemokine ligands that bind the receptor.

Samson 1996 (AV), Combadiere 1996 (AT3) and Raport 1996 (AW) each teach ligand binding to CCR5 amongst ligands MIP-1 alpha, MIP-1-beta and RANTES and note that the binding stimulates receptor function including calcium flux and chemotaxis within the second extracellular loop. Raport 1996 (AW) also notes that, "this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes," see in particular abstract noting others with direction to the N-terminus and second extracellular loop as important in mediating HIV infection.

Thus, the skilled artisan would be motivated to conduct the screening assay of Li et al., to generate antibodies that inhibit its specific ligands binding using the chemokine ligands MIP-1alpha, beta and RANTES as taught by Samson 1996 (AV), Combadiere 1996 (AT3) and Raport 1996 (AW) that are noted to be specific ligands of CCR5. That such assay would necessarily generate specificity to the second extracellular loop is evidenced by the intrinsic property that such is the site of ligand bidning at the receptor and that binding at such site is responsible for mediating calcium flux, chemotaxis and inhibition of HIV infection. Such assay is well within the skill of the artisan as taught by Li to select antibodies specific to inhibit binding and receptor function of CCR5, namely calcium flux and HIV infection, intrinsic properties of the ligand binding site, and thus the artisan would have an expectation of success in obtaining antibodies with these evidenced specific properties.

While the cumulative references teach that the ligand binding of MIP-1 alpha, beta and RANTES occurs at the second extracellular loop the references do not teach

that this specificity solely provides for the property of inhibition of HIV infection/entry. In contrast the literature notes that such properties are contributed by both the N-terminus and the second extracellular loop. Therefore a screen as in Li for inhibition of ligand binding and receptor function would necessarily result in the selection of antibodies specific to the second extracellular loop.

That these properties are intrinsic to antibodies that inhibit binding at the receptor and receptor function is further evidenced for example by Wu et al., 1997 IDS Reference (AS4), Atchison 1996, IDS Reference (AZ5) and Samson et al., J. Biol Chem., Oct. 1997, 272(40):24934-41.

Further, Raport (AW) notes that, "this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes," see in particular abstract noting others citation of the N-terminus and second extracellular loop as important in mediating HIV infection. This is in part separable from chemokine binding (with reference to the N-terminus), see in particular Atchison 1996, IDS Reference (AZ5). Further, that the Li chemokine binding region is within the second extracellular loop is further established via Wu 1997 (AS4) "The second extracellular loop of CCR5 is the major determinant of ligand specificity" and Samson, J. Biol Chem., Oct. 1997, 272(40):24934-41 "Multiple extracellular elements of CCR5 and HIV-1 entry: dissociation from response to chemokines." While evidence is of record that not all screening assays for HIV entry would achieve antibodies specific to the second extracellular loop, it is not the case for screening of inhibition of ligand binding or inhibition of receptor function such as calcium

flux. In contrast the art of record supports the conclusion that antibodies specific for inhibition of ligand binding and receptor function would be specific to the second extracellular portion and would also inhibit HIV binding/entry.

Accordingly, the screening assay of Li when practiced with MIP-1alpha, beta and RANTES ligands as suggested by Samson (AV), Combadiere (AT3) and Raport (AW) would necessarily result in the identification of antibodies specific to the second extracellular loop, i.e., the chemokine binding and signaling site. That this site is also evidenced as the major co-receptor allowing infection of HIV is further evidenced as noted via Samson 1997 and Atchison 1996 AZ5. Hence, the screening assay of Li would identify antibodies capable of inhibiting infection of HIV as the ligand binding site of the second extracellular loop is critical to HIV infection. Both properties are evidenced as mapping to the same site, i.e., within the second extracellular loop, see in particular Wu 1996 and 1997, Atchison, Samson 1996 and 1997, Raport and Combardiere.

Accordingly these references evidence that screening for antibodies that inhibit binding of ligands MIP-1 alpha, beta and RANTES would provide for antibodies specific to the second extracellular loop and that inhibit HIV infection/entry. Li teaches screening for antibodies specific to inhibit binding of ligand recognized in the prior art as MIP-1alpha, beta and RANTES as taught by Samson (AV), Combadiere (AT3) and Raport (AW). That such screening would necessarily result in the identification of antibodies directed to the second extracellular loop is an intrinsic result as that is the locale of the position of the ligand binding and a position that direct HIV entry, infection

and binding. Accordingly, the cumulative references fairly suggest the identification of antibodies exhibiting the delimited functional recitations absent factual evidence to the contrary. Antibodies specific to the ligand portion possess such properties as supported and evidenced in the art. No evidence is to the contrary.

With respect to the limitation of the antibody's ability to compete with the antibody of the accession, as the antibody has the same specificity, this is also an intrinsic property. The antibodies of same specificity would compete with each other for binding at the same site.

Accordingly the cumulative reference teachings render obvious the claimed invention.

Applicants traverse rejection as set forth throughout pp. 8-12 of the 7-3-06 response.

These arguments have been fully considered but are not persuasive. In particular, Applicants argue that Li does not present any working examples of antibodies to CCR5, nor guide to specific ligands or binding regions and therefore cannot teach or suggest the claimed limitations. In response, Li is not solely relied upon for these teachings. Li is on point to making antibodies to CCR5 that inhibit ligand binding **and** receptor function. The specifics of these characteristics are supplemented via alternative references that evidence the noted facts that MIP-1alpha, beta and RANTES are the ligands of CCR5 and that the ligands are evidenced to bind at the second extracellular loop. Li notes that known functions of the receptor include calcium flux and chemotaxis. These are the characteristics of mAb 2D7 disclosed in the specification

which is the basis for the recitation of antibodies that bind to the second extracellular loop of human CCR5. This is the only antibody documented that both inhibits ligand binding and receptor function and is specific to the second extracellular loop.

As in In re Wands, there is a high skill in the art with respect to antibody production. Accordingly, Li is not deficient in that it fails to evidence specific examples because the antigen specificity and noted functions in inhibiting ligand binding and receptor function are clearly set forth. Screening antibodies via these procedures are routine, and accordingly the antibodies with the same structural and functional specificity are suitably provided.

With respect to Raport (1996 and 1997), Combadiere and Samson (1996 and 1997), Applicants argue that these references do not teach or suggest the importance of the second extracellular loop and argue that Raport is silent with respect to portions of CCR5 mediating infection. In contrast, these references teach ligand binding specificity of CCR5. As set forth above, that this binding is evidenced at the second extracellular loop is evidenced by Wu et al., IDS Reference (AS4), Atchison, IDS Reference (AZ5) and Samson et al., J. Biol Chem., Oct. 1997, 272(40):24934-41. The abstract of Raport et al., J. Biol. Chem., 1996 July 19, Vol. 271(29):17161-166 is appended below.

> Chemokines affect leukocyte chemotactic and activation activities through specific G protein-coupled receptors. In an effort to map the closely linked CC chemokine receptor genes, we identified a novel chemokine receptor encoded 18 kilobase pairs downstream of the monocyte chemoattractant protein-1 (MCP-1) receptor (CCR2) gene on human chromosome 3p21. **The deduced amino acid sequence of this novel receptor, designated CCR5,** is most similar to CCR2B, sharing 71% identical residues. **Transfected cells expressing the receptor bind RANTES (regulated on activation normal T cell expressed), MIP-1beta, and MIP-1alpha with high affinity and generate inositol phosphates in response to these chemokines. This same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes (Cocchi, F., DeVico, A. L., Garzino-Demo, A., Arya, S. K., Gallo, R. C., and Lusso, P.(1995) Science 270, 1811-1815).** CCR5 is expressed in lymphoid organs such as thymus and spleen, as well as in peripheral blood leukocytes, including macrophages and T cells, and is the first example of a human chemokine receptor that signals in response to MIP-1beta.

Applicants may refer to that cited reference but need not as the specificity for HIV infection with respect to the second extracellular loop is moot as evidence by Wu et al., 1997, for example. The abstract is appended below.

> CCR5 is a chemokine receptor expressed by T cells and macrophages, which also functions as the principal coreceptor for macrophage (M)-tropic strains of HIV-1. To understand the molecular basis of the binding of chemokines and HIV-1 to CCR5, we developed a number of mAbs that inhibit the various interactions of CCR5, and mapped the binding sites of these mAbs using a panel of CCR5/CCR2b chimeras. One mAb termed 2D7 completely blocked the binding and chemotaxis of the three natural chemokine ligands of CCR5, RANTES (regulated on activation normal T cell expressed and secreted), macrophage inflammatory protein (MIP)-1alpha, and MIP-1beta, to CCR5 transfectants. This mAb was a genuine antagonist of CCR5, since it failed to stimulate an increase in intracellular calcium concentration in the CCR5 transfectants, but blocked calcium responses elicited by RANTES, MIP-1alpha, or MIP-1beta. This mAb inhibited most of the RANTES and MIP-1alpha chemotactic responses of activated T cells, but not of monocytes, suggesting differential usage of chemokine receptors by these two cell types. The 2D7 binding site mapped to the second extracellular loop of CCR5, whereas a group of mAbs that failed to block chemokine binding all mapped to the NH2-terminal region of CCR5. **Efficient inhibition of an M-tropic HIV-1-derived envelope glycoprotein gp120 binding to CCR5 could be achieved with mAbs recognizing either the second extracellular loop or the NH2-terminal region, although the former showed superior inhibition. Additionally, 2D7 efficiently blocked the infectivity of several M-tropic and dual-tropic HIV-1 strains in vitro. These results suggest a complicated pattern of HIV-1 gp120 binding to different regions of CCR5, but a relatively simple pattern for chemokine binding. We conclude that the second extracellular loop of CCR5 is an ideal target site for the development of inhibitors of either chemokine or HIV-1 binding to CCR5.**

It is true, as noted above that multiple sites are distinguished amongst CCR5 for binding and viral entry/infection, including the second extracellular loop. Nevertheless, the claims distinguish the antibody based upon its ability to bind the second extracellular loop, and this is the portion that binds ligand and mediates receptor function.

These findings are similar to those noted by Atchison, IDS Reference (AZ5) "Multiple extracellular elements of CCR5 and HIV-1 entry: dissociation from response to chemokines," and Samson, J. Biol Chem., Oct. 1997, 272(40):24934-41 "The second extracellular loop of CCR5 is the major determinant of ligand specificity". It is true that Wu, Atchison and Lopalco note other CCR5 sites that may bind HIV.

However, such does not indicate that screening for antibodies that inhibit ligand binding and receptor function would not also inhibit HIV infection as claimed. In fact the only antibody shown as in Wu 1997 to provide inhibition of ligand binding and receptor function was also evidenced to inhibit HIV entry. The antibody of the claims is noted with specificity for the second extracellular loop which is that site that mediates ligand binding and receptor function. The properties associated with the claimed antibody are noted to provide for the characteristics with respect to the wherein clauses regarding ligand binding, the functions of ligand binding and HIV infection or entry. Accordingly a screen for antibodies that inhibit ligand binding and function as suggested by Li would be expected provide antibodies with specificity to that site which is evidenced as the second extracellullar loop and which would further inhibit HIV infection and entry.

Applicants submit new evidence by Roschke et al., that show a panel of antibodies analyzed for CCR5 binding, inhibition of MIP-1β binding to transfected cells and inhibition of viral entry as in Figure 1. Applicants argue that the reference demonstrates that the ability to block chemokine binding and HIV infection were not mutually inclusive, noting that mAbs 20, 33, 37, 38 show low IC50 for inhibition of MIP-1Beta binding but do not inhibit entry of HIV.

This data is probative. However, the suggestion of Li was for selection of antibodies that inhibit binding of ligand **and receptor function**. Wu evidences that the only antibody that inhibited both ligand binding and receptor function was specific to the second extracellular loop and was evidenced to inhibit HIV entry. The Roschke reference does not distinguish amongst the antibodies tested for those that both inhibit

ligand binding and receptor function i.e., calcium signaling (flux) or chemotaxis. Accordingly, while some of the antibodies were noted to dissociate binding from HIV entry such is already known to occur. What is not distinguished by Roschke is if any of the antibodies that are noted to inhibit ligand binding also inhibit receptor function and whether these antibodies that inhibit both are dissociated from HIV binding and HIV entry.

Accordinlgy rejection stands for the same reasons of record. Li suggests to screen for CCR5 antibodies that inhibit ligand binding and receptor function and as supplemented by substantial secondary references, the art suggests that these antibodies are specific to the second extracellular loop and inhibit HIV entry. The single antibody representative of these characteristics provides a sound scientific basis for this conclusion. No evidence is provided to the contrary.

Conclusion

12. No claims are allowed.

13. 2D7 is the monoclonal antibody that is the basis for the recitations of the claims with respect to specificity for the second extracellular loop. The following references are noted with respect to 2D7 but are not relied upon for any rejection based upon the stipulations of 102(e) prior to the AIPA changes. WO 98/56421 discloses 2D7 at pp. 12 of the specification noting that 2D7 is a commercially available (Pharmingen, San Diego, CA) anti-CCR5 monoclonal antibody that inhibits HIV-1 entry. The Examiner has been unable to find other publicly available citation or reference to this Pharmingen antibody prior to the instant filing date. WO 97/47319 discloses 2D7 at p. 11, text with respect to Figure 7.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
9-13-06

SHARON TURNER, PH.D.
PRIMARY EXAMINER
9-13-06